

Module 4.1.

Role of Diet in Prevention and Treatment of Hyperlipidaemia in Children

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Learning Objectives

- To define the extent of morbidity and mortality caused by non-communicable diseases (NCD) and cardiovascular diseases (CVD);
- To present the pathogenesis of atherosclerosis, the main cause of morbidity and mortality among the NCD group;
- To describe the risk factors associated with CVD;
- To discuss the evidence on the relationship between risk factors in childhood and adult CVD;
- To present the prevalence of hyperlipidaemia/ hypercholesterolaemia in children;
- To examine the pro and cons for hypercholesterolaemia screening in children;
- To discuss the differential diagnosis of hypercholesterolaemia and hypertriglyceridaemia;
- To discuss the steps considered in the treatment of childhood hypercholesterolaemia;
- To present the nutrition-based measures which address hypercholesterolaemia at the population level and for high risk groups;
- To discuss the evidence behind the nutritional recommendations for the prevention and treatment of hypercholesterolaemia;
- To present other nutritional interventions that have been studied as adjunctive measures for the treatment of hypercholesterolaemia and hypertriglyceridaemia in children.

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Key Messages

- Studies have shown that atherogenesis early in life is associated with the traditional risk factors for CVD including hyperlipidaemia, overweight/ obesity, hypertension and diabetes;
- Selective screening for hyperlipidaemia has been advised by both the American Academy of Pediatrics and the American Heart Association in children with known risk factors or from families with known risk factors;
- Lifestyle modification is the mainstay of treatment and includes weight control, promotion of physical activity and nutritional intervention;
- In the general population, dietary recommendations should be consistent with good nutrition, aimed at a proper caloric balance while reducing intake of fat, cholesterol and trans fat;
- Dietary recommendations for an individualized approach in children at high risk include a proper caloric intake to ensure optimal growth and development, and further restriction of cholesterol and trans fats;
- With the increasing use of drugs in the treatment of children with hypercholesterolaemia, it must be emphasized that dietary and drug treatments are synergistic, and that dietary and lifestyle modifications must not be abandoned after the initiation of drug therapy.

1. Cardiovascular Disease, Background and Rationale

1.1 Non-communicable Diseases and Cardiovascular Disease Morbidity and Mortality

Non-communicable diseases (NCD) remain the leading cause of death and morbidity worldwide. According to WHO 2014 statistics about two thirds of the 58 million deaths that occur annually are caused by NCDs, comprising mainly cardiovascular diseases (CVD), cancers, diabetes and chronic lung diseases, and about a quarter of those who die are below 60 years of age. CVDs are the leading NCD and are responsible for over 17.5 million deaths per year (46.2% of NCD deaths), and thus are the leading causes of death worldwide. NCD are largely the result of high levels of behavioural risk factors (unhealthy diet, insufficient physical activity, smoking and harmful use of alcohol) and are generally preventable. Both population-wide measures and measures targeted on high risk groups can result in a major

reduction in the health and socioeconomic burden caused by these diseases and their risk factors (1, 2).

1.2 Atherosclerosis, Pathogenesis and Risk Factors

CVDs include diseases of the heart (ischaemic heart disease and coronary artery disease), vascular diseases of the brain (stroke) and diseases of blood vessels (hypertension and peripheral vascular disease). The underlying disease process in the blood vessels that causes ischaemic heart disease and stroke is atherosclerosis.

The Framingham cohort and subsequent studies have identified male gender, blood cholesterol, blood pressure, diabetes and smoking status as the major risk factors for CVD (3). **Table 1** presents a classification of the risk factors known to be involved in the development of atherosclerosis.

Table 1
Risk factors known to promote the development of atherosclerosis

Behavioural risk factors:

1. Unhealthy diet (rich in salt, fat and calories)
2. Sedentary lifestyle
3. Smoking
4. Alcohol excess

Metabolic risk factors:

5. Raised blood pressure (hypertension)
6. Raised blood sugar (diabetes)
7. Raised blood lipids (e.g. hypercholesterolaemia)
8. Overweight and obesity

Other risk factors:

9. Male gender
10. Inherited (genetic) disposition
11. Advancing age
12. Low socioeconomic status
13. Psychological factors (e.g. stress, depression)
14. Other risk factors (e.g. elevated homocysteine)

Atherosclerosis is an inflammatory process affecting medium-and large-sized blood vessels throughout the cardiovascular system. Sound data support the concept that inflammation and dyslipidaemia are both involved in the pathogenesis of atherosclerosis, from the early stages to the ultimate fate of the atheromatous plaque. The initial stage of atheroma formation in dyslipidaemia is increased endothelial cell (EC) transcytosis of plasma lipoproteins (Lp) (via a charge-mediated interaction with proteoglycans in the extracellular matrix) and their housing in the subendothelium. Within the subendothelium, Lp, especially low density lipoprotein cholesterol (LDL-C), become oxidized/modified Lp (mLp) which are highly atherogenic through their interaction with extracellular matrix components. In the presence of these changes, the EC initiates an inflammatory process manifested by the expression of new or more cell adhesion molecules, cytokines and chemokines. This is followed by the recruitment

of blood immune cells and initiation of a robust inflammatory reaction. Within the intima, monocytes become activated to macrophages that express scavenger receptors, which take up mLP and become foam cells that secrete a variety of proinflammatory mediators. The proliferation of intima-resident smooth muscle cells (SMC) and of SMC which have migrated from the media to the intima leads to the formation of a fibrous cap that is accompanied by increased synthesis of extracellular matrix components. Furthermore, resident and immune cells and the factors they secrete generate a calcified fibro-lipid plaque. The rupture of the unstable fibro-lipid plaque triggers thrombus formation that may partially or totally impede the blood flow, leading to myocardial infarction or stroke (4).

1.3 Risk Factors in Childhood: Determinants of CVD in Adulthood

All CVD risk factors, including abnormal lipid levels, often emerge during childhood and adolescence (5). The presence of multiple cardiovascular risk factors is associated with early acceleration of atherosclerosis (6). Early atherosclerotic lesions in children, adolescents and young adults, who died in accidents, have been shown to be significantly related to higher antecedent levels of total cholesterol (TC) and LDL-C, lower levels of high density lipoprotein-cholesterol (HDL-C), and other CVD risk factors, such as obesity, higher blood pressure levels, and cigarette smoking (6-8). Prospective, longitudinal studies have shown that risk factors levels measured in childhood are predictive of risk factor levels in adulthood. Several major prospective epidemiological studies from Muscatine (9), Bogalusa (10), the Coronary Artery Risk Development in Young Adults study (CARDIA) (11), the Pathobiological Determinants of Atherosclerosis in Youths study (PDAY) (12) and the Cardiovascular Risk in Young Finns Study (13), have shown that CVD risk factors in children and adolescents, particularly LDL-C and obesity, predicted clinical manifestations of atherosclerosis in young adults, as judged by carotid intima medial thickness (IMT), coronary artery calcium, or brachial flow-mediated dilatation (FMD).

Given its worldwide spread, obesity is predicted to become the next most common risk factor for atherosclerosis and CVD in adulthood. A longitudinal Israeli population study that included 2.3 million individuals who had their BMI measured at 16 to 19 years of age examined associations between childhood BMI and death from coronary heart disease, stroke, and sudden death from unknown cause, or a combination of all three categories (14). There was an increased risk of death from cardiovascular causes in individuals who had a childhood BMI in the 50th to 74th percentile, and the risk of death worsened with increasing BMI categories. When compared with the reference group (BMI 5th to 24th percentile), the obese group (BMI \geq 95th percentile) had a hazard ratio of 3.5 (95% CI, 2.9 to 4.1) for death from any cardiovascular causes. The 85th to 94th percentile BMI group had a hazard ratio of 2.3 (95% CI, 2.0–2.6) for total cardiovascular deaths. An earlier longitudinal Danish study also examined the association between BMI in childhood and coronary heart disease in adulthood (15). The study included 276,835 schoolchildren born from 1930 through 1976 who had BMI measured between 7 to 13 years old. Higher childhood BMI values increased the risk for having a coronary heart disease event in adulthood.

1.4 Metabolic Syndrome, an Emerging Cardiovascular Disease Risk Factor

The metabolic syndrome (MetS) is a cluster of cardiometabolic risk factors associated with an increased risk of developing CVD and diabetes mellitus (16). The prevalence of the MetS is not particularly high in the overall paediatric population (3%-4%) but it is as high as 30%-50% among overweight youth (17). The National Cholesterol and Education Program (NCEP) definition of the metabolic syndrome for adults is presented in **Table 2**. Currently, there is no accepted definition of the metabolic syndrome for children and adolescents. It has been recommended that the five key MetS variables to be used for the calculation of the MetS score include: central obesity, low HDL-C, elevated triglycerides (TG), elevated BP, and abnormal glucose metabolism (18). Furthermore, the individual components should be age-standardized (and maturity-standardized, if available) given the influence of growth and maturation on the development of the metabolic risk factors. MetS is diagnosed in the presence of any 3 of the 5 features.

Table 2
Metabolic syndrome definition/ criteria in adults and children

Clinical parameter	Adult definition of MetS	Paediatric MetS score*
Central obesity	Waist circumference > 102 in male > 88 in women	Waist circumference or BMI or Skin fold thickness
Lipids level	Triglycerides, > 150mg/dL HDL, < 40mg/dL in male or HDL, < 50mg/dL in women	Elevated triglycerides Low HDL
Blood pressure (BP)	≥ 130/85 mmHg	Elevated BP (systolic and/or diastolic and/or MAP)
Abnormal glucose metabolism (includes diabetes)	Fasting glucose level > 100mg/dl	Abnormal glucose metabolism (impaired fasting glucose, impaired glucose tolerance, and/or HOMA)

* All components should be adjusted for age and gender (and puberty stage, if available)

Follow up of 5 to 19 year old children enrolled in the Lipid Research Clinics (LRC) Princeton Prevalence Study from 1973 to 1976 and analysis of data from the Princeton Follow-up Study (2000–2004) found that paediatric MetS was predictive of both adulthood MetS and T2DM (18). Furthermore, the Princeton Follow-up Study identified 17 cases of CVD. The incidence of CVD during the intervening years for the 31 patients with paediatric MetS was 19.4% ($n=6$), compared with 1.5% for subjects without MetS as children. In multivariate logistic analyses, paediatric MetS (OR: 14.7; $P < 0.0001$) and age (OR: 1.2; $P < 0.03$) were significant predictors of CVD (19).

1.5 Prevalence of Dyslipidaemia in Children and Adolescents

The prevalence of lipid abnormalities in children is increasing, primarily in association with the concomitant obesity epidemic and the MetS. The National Health and Nutrition Examination Survey (NHANES) for 2011–2014 reported that 21.0% of children and adolescents in the

United States had at least one lipid abnormality. The prevalence of abnormal TC ≥ 200 mg/dL (5.2 mmol/l) was 7.4% in 6 to 19 years old, but higher in adolescents (8.9%), girls (8.9%), non-Hispanics Asians (10.9%) and the obese (11.6%). Low HDL-C ≤ 35 mg/dL (0.9 mmol/l) was reported in 13.4%, but higher (18.4%) for adolescents aged 16–19, boys (14.8%), non-Hispanic white (14.4%) or Hispanic (15.6%) children and adolescents, and with increasing BMI, 33.2% with BMI $>95\%$. The overall prevalence of high non-HDL cholesterol [non-HDL-C ≥ 130 mg/dL (3.4 mmol/l)] among children and adolescents was 8.4%, higher in girls (9.4%), and with increased BMI, 16.7% among overweight children and adolescents (20).

Limited information is available on the epidemiology of hypertriglyceridaemia (HTG, triglycerides >150 – 499 mg/dL; 1.65 – 5.5 mmol/l) and severe HTG (SHTG, triglycerides >500 mg/dL; >5.5 mmol/l) in children. Using data from NHANES 2001–2008 and the i3 InVision Data Mart database it was estimated that 10% of US children have elevated TG levels; 10.5% of children have TG levels of 150 to 499 mg/dL, and 0.2% of children have TG levels ≥ 500 mg/dL. Factors statistically significantly associated with having HTG or SHTG in the Data Mart database were: being male, 12 to 19 years old, having high LDL-C, having low HDL-C, diabetes, and psychological disorders (21).

The 2014 update from the American Heart Association (AHA), in conjunction with the Centers for Disease Control and Prevention and the National Institutes of Health statistics reported that 31.8% of 2 to 19 years old children are overweight and obese (which represents 23.9 million children) and 16.9% are obese (12.7 million children). From 1971–1974 to 2007–2010, the prevalence of obesity in children 6 to 11 years of age has increased from 4.0% to 18.8% (22).

1.6 Screening for Hyperlipidaemia in Children: pro and cons

Individuals in early adulthood with untreated familial hypercholesterolaemia (FH) are nearly 100 times more likely than unaffected individuals to develop coronary artery disease. As children with hypercholesterolaemia do not generally present any complaints or symptoms, paediatric organizations have developed different screening strategies to identify such children. There are two main screening methods: universal screening and selective screening. Universal screening means screening of the whole population. Selective screening means screening a part of the population, based on certain selection criteria. Selective screening may be based on a family history of affected relatives (dyslipidaemia or premature CVD) or family cascade screening (lipid or genetic cascade screening). FH fulfils most of the WHO disease criteria for screening; however, screening strategies to identify FH patients are still an issue of debate.

Based on the NCEP 1992 report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents, the American Academy of Pediatrics (AAP) recommend in 2007 selective screening for children and adolescents in the following high risk groups (**Fig. 1**) (23, 24):

- 1) Positive family history of dyslipidaemia OR;
- 2) Positive family history of premature CHD OR;
- 3) Unknown family history OR;

- 4) Children with other CVD risk factors (overweight/obesity, hypertension, cigarette smoking) or disorders that affect lipoprotein metabolism (endocrine, genetic, metabolic, renal or liver disorders).

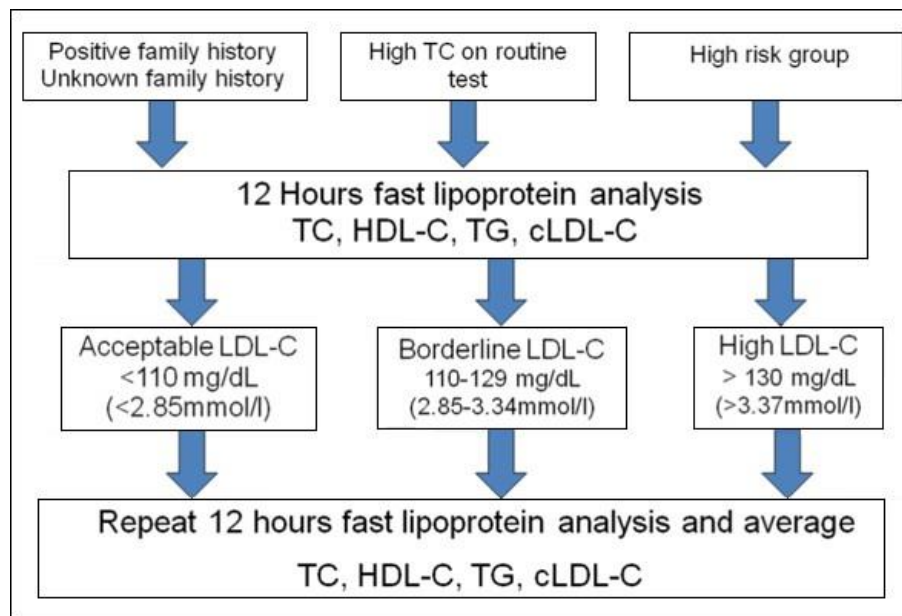


Fig. 1. Algorithm for selective screening for hypercholesterolemia

At that time, the AAP recommendations were in agreement with the American College of Obstetricians and Gynecologists for screening in adolescents and the American Heart Association (AHA) from 2003, updated in 2007 (25, 26).

The National Lipid Association (NLA) recommended, however, at their Annual Scientific Session in May 2011, universal screening for children 9 to 11 years old and selective screening, starting from age 2 in children with CAD risk factors (27). Furthermore, in 2011, an expert panel from the National Heart, Lung, and Blood Institute (NHLBI) recommended universal lipid screening for children on 2 occasions, first between 9 and 11 years of age and again between 17 and 21 years of age (28). The release of the 2011 NHLBI guidelines re-ignited significant controversy in the medical and popular press about whether and how to screen for paediatric lipid disorders.

Among a national, randomly selected sample of 614 out of 1627 practicing AAP physicians, 68% reported they never/rarely/sometimes screened healthy 9- to 11-year-olds but more providers screened based on family cardiovascular history (61%) and obesity (82%). Only 58% agreed with universal screening, and 23% felt screening was low priority. Although 62% and 89% believed statins were appropriate and safe for children and adolescents with high LDL-C (200 mg/dL) unresponsive to lifestyle, only a minority initiated statins (8% and 21%) (29).

The last systematic review published in 2016 of the evidence on benefits and harms of universal screening adolescents and children for heterozygous FH from the US Preventive Services Task Force (USPSTF) concluded that universal screening can detect FH and lipid-lowering treatment in childhood can reduce lipid concentrations in the short term, with little

evidence of harm. However, there is no evidence for the effect of screening for FH in childhood on lipid concentrations or cardiovascular outcomes in adulthood, or on the long-term benefits or harms of beginning lipid-lowering treatment in childhood (30).

Similarly, no direct evidence was found for the effect of screening for multifactorial dyslipidaemia, on dyslipidaemia and atherosclerosis in childhood or on MI and ischaemic stroke in adulthood (31).

The pros and cons for both selective and universal screening are presented in **Table 3**.

Information on costs of screening for FH and MetS in youth in the United States is incomplete. A cascade screening programme for FH in the Netherlands demonstrated that for every 100 people treated, 26 myocardial infarcts were prevented, and there was an average lifetime cost of \$8700 per year gained (32). Therefore, economic considerations are relevant and additional studies will hopefully help to properly project estimates of paediatric universal screening, evaluation, and treatment.

Table 3
Selective and universal screening for dyslipidaemia: pros and cons

Selective screening		Universal screening	
Pros	Cons	Pros	Cons
Cardiovascular (CV) health in childhood predicts optimal CV outcomes in adulthood	Concerns of misinterpretation of screening results	Unreliable family history and low sensitivity of selective screening	No direct evidence that interventions in children prevent CVD in adults
Statin treatment of children and adolescents with FH normalizes FMD and regresses carotid IMT	Concern about unjustified use of medication	The atherosclerosis lesion begins in childhood	May improperly label children as having high cholesterol levels
Use of statins in children with FH of up to 2 years showed no adverse effects on growth, development, cognition, or sexual maturation		Lipids levels track from childhood to adulthood	Harmful effects of restrictive diets
		Intervention in children changed surrogate markers such as CIMT, FMD	Expensive
		Lifestyle changes are easier in childhood	

The AHA recommends screening children above 2 years of age with a fasting lipid profile and taking an average of the results of three fasting lipid profiles. If values are above reference ranges, cardiovascular risk reduction interventions are recommended (26).

A recent meta-analysis of published data on lipid values in FH individuals showed that LDL-C measured after 1 year of age and before puberty had better discrimination than at other ages, detecting 96% of those with FH at a false-positive rate of 1% (33). A study of 1034 children from FH kindreds showed that an LDL-C level > 135 mg/dL (>3.5 mmol/L) predicted genetically confirmed FH with a 0.98 post-test probability (34).

The NCEP-recommended levels for identifying children and adolescents with abnormal lipid and lipoprotein concentration are based on the Lipid Research Clinic Paediatric Prevalence Study data and are the same for all children from 2 to 18 years age (**Table 4**) (35). Recently,

data from the NHANES 1988-2002 were used to develop age- and gender-specific thresholds that can be used to define abnormal levels of TC, LDL-C, HDL-C, and triglycerides for 12 to 20 year olds (36).

Table 4

Lipid profile for children 2 to 18 years old according to NCEP guidelines (Lipid Research Clinic Pediatric Prevalence Study) (18).

Lipoproteins	Acceptable (mg/dL) (mmol/l) <75th percentile	Borderline (mg/dL) 75th - 95th percentile	Elevated (mg/dL) >95th percentile
Total Cholesterol	<170 (4.4)	170-199 (4.4-5.2)	>200 (>5.2)
LDL-Cholesterol	<110 (2.9)	110-129 (2.9-3.4)	>130 (>3.4)
HDL-Cholesterol	>45 (1.2)	NA	NA
Triglycerides	<100 (1.1)	100-124 (1.1-1.4)	>125 (>1.4)

2. Evaluation and Management of Hyperlipidaemia in Children

2.1 Familial Hypercholesterolaemia: Diagnosis and Differential Diagnosis

Familial hypercholesterolaemia (FH) is an inherited autosomal dominant (AD) disorder resulting from a reduction in the capacity to clear LDL from the circulation. About 79% of cases are caused by defects in the low density lipoprotein-receptor (LDL-R) gene. Worldwide, more than 2000 different mutations in the LDL-R gene have been characterized and linked to a hypercholesterolaemic phenotype. Defects in the genes for apolipoprotein B (Apo B) and proprotein convertase subtilisin/kexin type 9 (PCSK9) account respectively for about 5% and less than 1% of cases of AD hypercholesterolaemia (37). A very rare recessive form of FH is caused by mutations in low-density lipoprotein receptor adaptor protein 1 (LDLRAP1). The remaining 15% of FH cases are either polygenic or are driven by monogenic mutations whose prevalence is not yet determined (38).

The genetic defects in FH result in reduced LDL-cholesterol (LDL-C) uptake and clearance by liver cells, increased serum total- and LDL-C levels and increased risk of developing premature CHD. Inheritance of a defective gene from one parent causes heterozygous FH (HeFH); defective genes from both parents cause homozygous FH (HoFH). HeFH is fairly common with an estimated incidence of 1 per 200-500 births in many western populations, while HoFH is a rare disease with an estimated incidence of one per million. The prevalence is known to be higher in certain regions where a founder gene effect has occurred and most FH patients are carriers of one of a few mutations; Afrikaners in South Africa and French Canadians provide examples, where the carrier frequency has been estimated to be 1/70 and 1/200 respectively. Untreated HeFH carries an about 80-fold risk of death from CHD in the 20–39 years age group. HoFH carries an extremely high risk and most of the untreated individuals will have coronary or cardiovascular disease (CVD) in childhood or adolescence (39).

Molecular DNA testing is the most reliable method of diagnosing FH. Diagnosis, however, is usually done clinically by using a validated set of criteria (MEDPED, the Dutch Lipid Clinic

Network or the Simon Broome Registry in the UK (40-43)) (**Table 5**). The Simon Broome Register criteria take into account that total C and LDL-C levels differ for adults and children, and the age of CVD in family members. The clinical diagnostic criteria for FH are: 1) elevated cholesterol level in the patient, 2) presence of tendon xanthomata in the patient or first degree relative, and 3) a dominant pattern of inheritance of premature coronary heart disease or elevated cholesterol. Using this approach, cases are categorized as 'definite' and 'possible'. In the 1994 revision 'DNA-based evidence of an LDL-receptor mutation or familial defective apoB-100' was also added as sufficient for a 'definite' diagnosis (41).

A similar diagnostic tool has been developed by the Dutch Lipid Clinic Network. This includes similar features to the Simon Broome criteria, but adds the calculation of a numeric score (42). The main difference between the Dutch scoring system and the Simon Broome Register criteria is the requirement of the latter for tendon xanthomata to be present for a 'definite' diagnosis of FH to be made (if a LDL-R mutation has not been identified).

Table 5
Simon Broome Registry, the Dutch Lipid Clinic Network and MEDPED criteria for diagnosis of FH

Simon Broome Register group definition of FH	Dutch Lipid Clinic network diagnosis of FH	The US (MEDPED) diagnostic criteria for FH
Definite diagnosis of FH a)TC ≥ 7.5 mmol/L (290mg/dL) in adults or TC ≥ 6.7 mmol/L (260mg/dL) in children <16 years OR LDL-C ≥ 4.9 mmol/L (160mg/dL) PLUS b)Tendon xanthomas in patient or relative (1 st or second degree) OR c)DNA-based evidence of an FH causing mutation	Family history A.1 st degree relative with premature (<55 years in men and <60 years in women) coronary or vascular disease (1) B.1 st degree relative with LDL-C $\geq 95\%$ percentile and/or A.1 st degree relative with tendon xanthoma and/or arcus corneus B.Children below 18 years with LDL-C $\geq 95\%$ percentile	Age < 20 years 1 st degree relative with FH, TC ≥ 5.7 mmol/L (220mg/dL) 2 nd degree relative with FH, TC ≥ 5.9 mmol/L (228mg/dL) 3 rd degree relative with FH, TC ≥ 6.2 mmol/L (239mg/dL) General population TC ≥ 7.0 mmol/L (270mg/dL)
Possible diagnosis of FH defined as a) above and d) or e) d)Family history of myocardial infarction before age 50 in 2 nd degree relatives or before 60 years in 1 st degree relatives e)Family history of hypercholesterolemia in 1 st degree relatives or TC levels ≥ 7.5 mmol/L (290mg/dL) in 2 nd degree relatives.	Clinical history A.Patient has premature (<55 years in men and <60 years in women) coronary artery disease (2) B. Patient has premature (<55 years in men and <60 years in women) cerebral or peripheral vascular disease (1)	Age 20-29 years 1 st degree relative with FH, TC ≥ 6.2 mmol/L (239mg/dL) 2 nd degree relative with FH, TC ≥ 6.5 mmol/L (251mg/dL) 3 rd degree relative with FH, TC ≥ 6.7 mmol/L (258mg/dL) General population TC ≥ 7.5 mmol/L (289mg/dL)

	Physical Examination Tendon xanthomas (6) Arcus corneus below age 45 (4)	Age 30-39 years 1 st degree relative with FH, TC \geq 7.0mmol/L (270mg/dL) 2 nd degree relative with FH, TC \geq 7.2mmol/L (278mg/dL) 3 rd degree relative with FH, TC \geq 7.5mmol/L (289mg/dL) General population TC \geq 8.8mmol/L (340mg/dL)
	Laboratory data LDL-C > 8.5mmol/L (330mg/dL) (8) LDL-C 6.5- 8.4mmol/L (259-329mg/dL) (5) LDL-C 5.0-6.4mmol/L (190-249mg/dL) (3) LDL-C 4.0-4.9mmol/L (155-189mg/dL) (1)	Age >40 years 1 st degree relative with FH, TC \geq 7.5mmol/L (289mg/dL) 2 nd degree relative with FH, TC \geq 7.8mmol/L (301mg/dL) 3 rd degree relative with FH, TC \geq 8.0mmol/L (309mg/dL) General population TC \geq 9.3mmol/L (359mg/dL)
	DNA analysis Functional mutation in LDLR	

2.2 Hyperlipidaemia: Differential Diagnosis

The differential diagnosis of hyperlipidaemia in children is extensive and includes primary and secondary lipid disorders (**Table 6** and **Table 7**) (28, 44).

Table 6
Lipid profile and known molecular defects responsible for primary hyperlipidaemias

Disease	Lipid profile, elevated*	Molecular defect
FCH, familial combined hyperlipidaemia	TC, TG, CM	<i>LPL</i> , lipoprotein lipase; <i>APOC2</i> , apolipoprotein C2
FH, familial hypercholesterolaemia	TC, LDL-C	<i>LDLR</i> , LDL receptor; <i>APO</i> , apolipoprotein B; <i>PCSK9</i> , proprotein convertase subtilisin/kexin type 9; <i>LDLRAP1</i> , low-density lipoprotein receptor adaptor protein 1
FHC, familial hyperchylomicronaemia	TC, TG, LDL-C	<i>APOA5</i> , apolipoproteinA5 common SNPs

DBL, dysbetalipoproteinaemia	TC, TG, IDL-C	<i>APOA5</i> , apolipoproteinA5 common SNPs <i>APOE</i> , apolipoprotein E common SNPs
FHTG, familial hypertriglyceridaemia	TC, TG, CM	<i>APOE</i> , apolipoprotein E common SNPs
MHL, mixed hyperlipidaemia	TC, TG, CM	<i>LPL</i> , lipoprotein lipase; <i>APOC2</i> , apolipoprotein C2 <i>APOA5</i> , apolipoproteinA5 common SNPs <i>APOE</i> , apolipoprotein E common SNPs
TD, Tangier disease	TG, low TC, LDL-C, HDL-C	<i>ABCA1</i> , ATP-binding cassette A1
LCAT deficiency	TG, low TC, LDL-C, HDL-C	<i>LCAT</i> , lecithin cholesterol acyltransferase
HLD, hepatic lipase deficiency	TC, TG, LDL-C, HDL-C, IDL-C	<i>LIPC</i> , hepatic lipase
CETPD, CETP deficiency	TC, TG, HDL-C	<i>CETP</i> , cholesteryl ester transfer protein
SITO, sitosterolaemia	TC, LDL-C, low HDL-C	<i>ABCG5/G8</i> , ATP-binding cassette transporter G5/G8
Cerebrotendinous Xanthomatosis (CTX)	TC, xanthomas	<i>CYP27A1</i> , 27 hydroxylase
Wolman disease Cholesteryl ester storage disease	LDL-C, liver disease	<i>LIPA</i> , lysosomal acid lipase

*C, cholesterol; TC, total cholesterol; LDL-C, low-density lipoprotein C; HDL-C, high density lipoprotein C, TG, triglycerides; CM, chylomicrons

Table 7
Differential diagnosis of secondary hyperlipidaemias

Group of Disorders	Diseases
Endocrine	Diabetes mellitus, hypothyroidism, hypopituitarism, insulin resistance
Metabolic	Obesity, lipodystrophy, alcohol, anorexia, bulimia, porphyria
Storage disorders	Glycogen storage disease, Niemann-Pick, Tay-Sachs
Hepatic disorders	Cholestatic disorders
Renal diseases	Chronic renal failure, nephrotic syndrome, haemolytic uraemic syndrome
Chronic inflammatory	Systemic lupus erythematosus, juvenile rheumatoid arthritis disorders
Drugs	Androgens, glucocorticoids, calcineurin inhibitors, retinoids, oral contraceptives
Others	Pregnancy, Klinefelter syndrome, idiopathic hypercalcaemia, aemophagocytic syndrome

2.3 Goals of Hyperlipidaemia Treatment

Hypercholesterolaemia is an established risk factor for the development of atherosclerosis. Other major CHD risk factors and risk equivalents in children include family history of premature heart disease, overweight/obesity, hypertension, diabetes, smoking, and reduced HDL-C concentration. In 2006, a group of experts from the AHA Expert Panel on Population and Prevention Science, endorsed by AAP, selected 8 paediatric medical conditions known to make the paediatric patient at high risk for both lipoprotein abnormalities and CVD, including: 1) familial hypercholesterolaemia; 2) diabetes mellitus, type 1 and type 2; 3) chronic kidney disease; 4) heart transplantation; 5) Kawasaki disease; 6) congenital heart disease; 7) chronic inflammatory disease; and 8) childhood cancer. A stratification protocol was established and recommendations for cardiovascular risk identification and reduction specific to each disease setting were developed and published (**Table 8**) (45).

Table 8
Cardiovascular risk stratification and recommendations for high risk paediatric disorders

Tier/Risk classification	Medical conditions	Tier specific cut-points/ treatment goals
Tier I, High risk Manifest CVD < 30 years Clinical evidence	Homozygous FH Diabetes mellitus, type 1 Chronic kidney disease/ end stage renal disease Post heart transplantation Kawasaki disease with current coronary aneurysms	BMI ≤ 85% for age and gender BP ≤ 90% for age and gender LDL-C ≤ 100 mg/dL; 2.6mmol/L FG < 100 mg/dL; 2.6mmol/L; HbA1C < 7%
Tier II, Moderate risk Accelerated atherosclerosis Pathophysiological evidence	Heterozygous FH Kawasaki disease with regressed coronary aneurysms Diabetes mellitus, type 2 Chronic inflammatory disease	BMI ≤ 90% for age and gender BP ≤ 95% for age and gender LDL-C ≤ 130 mg/dL; 3.4mmol/L FG < 100 mg/dL; 2.6mmol/L; HbA1C < 7%
Tier III, At risk High risk setting for accelerated atherosclerosis Epidemiological evidence	Post-cancer-treatment survivors Congenital heart disease Kawasaki disease without coronary involvement	BMI ≤ 95% for age and gender BP ≤ 95% +5mmHg for age and gender LDL-C ≤ 160 mg/dL; 4.2mmol/L FG < 100 mg/dL; 2.6mmol/L HbA1C < 7%

2.4 Management Plan for Hyperlipidaemia

Primary care clinicians should be responsible for screening and diagnosis. For treatment of children with FH, either consultation with or referral to a lipid specialist is recommended. Comprehensive cardiovascular risk assessment and management is critical. The baseline evaluation of children with hyperlipidaemia is detailed in **Table 9** and **Fig. 2** (46).

Table 9
The baseline evaluation and management plan of children with hyperlipidaemia

- **Family pedigree as complete as possible with specific enquiries on:**
 - Known CVD risk factors for adults: overweight, hypertension, diabetes
 - All CVD manifestations: MI, angina pectoris, cardiac arrhythmias, sudden cardiac death, cardiac failure, documented atherosclerosis, cerebrovascular disease, peripheral arterial disease
 - All causes of death: age and causes
- **Personal medical history and lifestyle including:**
 - All disorders known to be associated with dyslipidaemia and an increased risk of CVD, as listed
 - Record the degree of physical activity and habits: smoking, drinking
- **Lipoprotein profile of all immediate family members**
- **Physical examination with especial attention to:**
 - Stigmata of FH: xanthomas, arcus corneus, thickening of tendon of Achilles
 - Measurement of BP
 - Evaluation of pubertal status
- **Blood chemistry, thyroid function and other investigations according to the medical history and physical examination**
- **Nutritional evaluation including:**
 - Three day food diary
 - Anthropometry, weight, height and plotting on growth curves
 - Body composition assessment (MAC, TSFT, BMI) .
- **Baseline non-invasive assessment of vascular changes:** Carotid IMT, Brachial FMD
- **Decide on treatment goals and plan**
- **Follow-up**

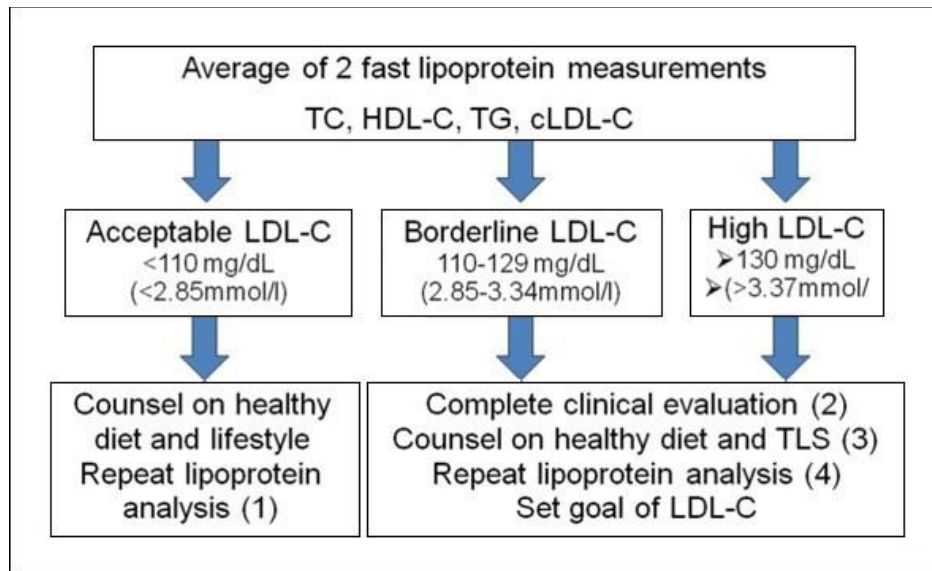


Fig. 2 Algorithm for investigation, treatment and follow up (1)

The lipid linked cardiovascular risk is principally determined by the concentrations of LDL-C, and of HDL-C (inversely); as concentrations of blood TC and LDL-C increase so does the risk of cardiovascular disease (CVD). Systematic reviews and meta-analyses in adults have shown that lowering of cholesterol whether by diet, drugs, or other means, decreases CVD risk (47). The treatment goal of lipid lowering therapy in paediatric FH patients is a $\geq 30\%$ reduction in LDL cholesterol or LDL cholesterol ≤ 130 mg/dL/3.4mmol/L. More aggressive LDL cholesterol targets should be considered for those with additional cardiovascular risk factors or conditions (as presented in **Table 8**).

2.5 Therapeutic Life Style Changes

The Adult Treatment Panel III, published in 2001, recommends a multifaceted lifestyle approach to reduce risk for CHD (16). This approach is designated therapeutic lifestyle change (TLC). Its essential features are:

- Reduced intakes of saturated fats (<7% of total calories) and cholesterol (<200 mg/d)
- Therapeutic options for enhancing LDL lowering such as plant stanols/sterols (2 g/d) and increased viscous (soluble) fibre (10-25 g/d)
- Weight reduction
- Increased physical activity

The first formal institutional recommendation on risk factors in children came from the Committee on Nutrition of the AAP and focused on diet as a means of controlling plasma cholesterol levels in children with FH (48). The AHA made a similar recommendation in 1978 and expanded the application to all types of dyslipidaemia (49). The current treatment strategies have been laid out in the comprehensive report of the 1992 NCEP Expert Panel on Children and Adolescents and although this dates from almost two decades ago, these guidelines are still the basis for the present recommendations of AAP and AHA, with

therapeutic lifestyle changes, including dietary modification, physical activity and weight control as the first line of treatment for all childhood dyslipidaemia (48-50).

3. Nutritional Intervention for the Prevention and Treatment of Hyperlipidaemia

3.1 Nutrition and Hypercholesterolaemia: the Evidence

Lipid-enriched diets are often used to induce or accelerate the rate of progression of atherosclerosis in murine models. By far, the most widely used high-fat diet for atherosclerosis experiments is the so-called Western-type diet, which contains 21% fat and 0.15% cholesterol. As for the opposite, regression of pre-existing atherosclerotic lesions has also been demonstrated in mouse models of atherosclerosis after switching to a chow diet (51). In monkeys with severe atherosclerosis, regression of atherosclerosis occurred when blood cholesterol level was lowered with diet and drugs (51).

Epidemiological studies have shown that, in humans, the major nutritional determinant of differences in serum cholesterol levels between countries appears to be the proportion of saturated fat in the diet. Total blood cholesterol levels in children vary geographically. In countries such as the Philippines, Italy, and Ghana where saturated fat constitutes approximately 10% of the dietary intake, the serum cholesterol levels in boys 8 to 9 years of age are generally below 160 mg/dL (4.2 mmol/L). In boys from countries such as the Netherlands, Finland, and the United States, the saturated fat intake varies from 13.5% to 17.7% of energy intake, and serum cholesterol levels are generally around 160 mg/dL (4.2mmol/L).

3.2 Dietary Intervention: Human Studies

The principal goal of dietary treatment of hypercholesterolaemia is the reduction of the plasma LDL-C. This is best accomplished by enhancing the activity of LDL receptors and, at the same time, depressing liver synthesis of cholesterol. Both cholesterol and saturated fat down-regulate the LDL receptor and inhibit the removal of LDL from the plasma by the liver. Saturated fat down-regulates the LDL receptor, especially when cholesterol is concurrently present in the diet. The total amount of dietary fat is also important. The greater the flux of chylomicron remnants into the liver, the greater is the influx of cholesterol ester. In addition, factors that affect LDL synthesis could be important. These include excessive calories (obesity) that enhance very low density lipoprotein (VLDL) and, hence, LDL synthesis, and mono- and polyunsaturated fatty acids. Therefore, the optimal, classic diet for treatment of children and adults has the following characteristics: low fat (25-35% kcal), saturated fat (less than 7% kcal) and cholesterol (less than 200mg) and replacement with fat from omega-6 polyunsaturated and mono-unsaturated fat, carbohydrate (55-65% kcal), and protein (15-25% kcal).

Low-saturated fat, low-cholesterol diets in adults have been shown to lower LDL-C by an average of 12%, with a 1.9-mg/dL (0.05 mmol/L) decline in LDL-C for every 1% decline in saturated fat (52,53). Further restricting saturated fat from 10% of total energy to 7% (the Therapeutic Lifestyle Change diet) increased the LDL-C reduction to 16%. Adult studies have

shown that, depending on age, a reduction of cholesterol levels by 10%, decreases the incidence of CAD by 54% at age 40 years, 39% at age 50, 27% at 60, 20% at 70, and 19% at 80 (47).

Since 1983 the Cardiovascular Disease in the Young Council of the AHA has recommended reduction of dietary fat and salt for all children to control serum lipids and blood pressure. These recommendations were echoed by the American Academy of Pediatrics in 1986 and the NCEP in 1992 (54, 55).

Paediatric studies confirmed the results of the adult reports, showing safety and efficacy of a low-cholesterol and low-saturated fat diet, at both clinical and school-based levels. In 1972, teenage boys in a New England boarding school lowered their mean serum cholesterol concentration (14%) after consuming a fat-modified diet (56). A fat-modified diet produced a nearly identical result in Finnish children 8 to 18 years of age in 1986. Intensive intervention in schools to change diet among 13- to 15-year old adolescents reduced serum cholesterol levels by 0.5 mmol/L (19 mg/dL) (57).

The Dietary Intervention Study in Children (DISC) was a controlled trial started in 1987 and conducted over 3 years in US children, 8 to 11 years old with high LDL-C (80th-90th percentile) (58-60). The children were randomized to an intervention group (n=334) receiving a diet with 28% of energy from total fat, 8% from saturated fat, up to 9% from polyunsaturated fat, and less than 75 mg cholesterol per 1,000 kcal per day and to a control group on regular care (n=329) that consumed 33% to 34% of calories as total fat, 12.7% of calories as saturated fat, and 112 mg per day of cholesterol. Reductions in dietary total fat, saturated fat, and cholesterol were greater in the intervention than in the usual care group throughout the intervention period. At 1 year, 3 years, 5 years and at the last visit (7.5 years), the intervention compared with the usual care group had 4.8 mg/dL, 3.3 mg/dL, 2.8 mg/dL and 2.0 mg/dL lower LDL-C, ($P < .001$ and $P < .02$, at 1 and 3 years, but not at 5 years ($P = .11$) or at the last visit ($P = .25$) respectively. There were no differences at any data collection point in sexual maturation, height or BMI.

A follow-up study conducted in 2006–2008 in 230 (76%) DISC female participants 25–29 yr old that were not under any dietary restrictions during the 9 years from the termination of DISC study showed that the former intervention group participants had lower BP and fasting glucose as well as lower concentrations of large very-low-density lipoprotein particles (60).

In conclusion, dietary fat modification can be achieved and safely sustained in actively growing children with elevated LDL-C, and elevated LDL-C levels can be improved significantly for up to 3 years. Although not sustained in time, consumption of a diet lower in fat and higher in fiber during childhood and adolescence may benefit glycaemic control and blood pressure in long term.

The Special Turku Coronary Risk Factor Intervention Project (STRIP), it is the only randomized trial examining the health effects of reduced saturated fat diet in healthy individuals from infancy to young adulthood (61). A low saturated fat, low cholesterol diet was introduced to healthy infants in the intervention group (n=540) begun at weaning (age 7 months) with parental dietary education continued through the age of 7 years. The intervention was individualized for each child and aimed at achieving a fat intake of 30% to 35% of daily energy, with a ratio of saturated to monounsaturated plus polyunsaturated fatty acid of 1:2 and cholesterol intake <200 mg/d. The control children (n=522) received the basic health education routinely given at Finnish well-baby clinics and through school health care. A low

saturated fat, low cholesterol-oriented nutrition intervention had a favourable effect on saturated fat intake and serum total and LDL-C concentrations throughout the first 14 years of life. Boys had lower total and LDL-C concentrations than girls throughout childhood ($P < 0.001$), and the intervention effect on serum cholesterol concentration was larger in boys than girls. The 2 study groups showed no difference in growth, BMI, pubertal development, or age at menarche (median, 13.0 and 12.8 years in the intervention and control girls, respectively; $P < 0.52$), indicating that a low-fat diet under medical supervision may be instituted safely and effectively after 6 months of age (62-65).

Further data from participants in the STRIP study showed that BMI, BP, LDL-C, and homeostasis model of IR identified since childhood associate with arterial distensibility in healthy children and adolescents, supporting the relevance of these factors as part of primordial prevention beginning in childhood (66).

An additional study, the Parent-Child AutoTutorial (PCAT) program reported 8% improvement in LDL-C level compared with the at-risk control group ($P < 0.05$) (67).

In conclusion, trials of dietary intervention have shown that the low-fat, low-cholesterol diet recommended by the National Cholesterol Education Program in 1992 report is safe and thus can be implemented in population-based strategies to lower cardiovascular disease risk.

Low carbohydrate diets have been proved to be effective alternatives to low-fat diets for weight loss, and have shown even more favourable effects on lipid profile and on glycaemic control in overweight adults (68). The efficacy of low carbohydrate diets in children with hypercholesterolaemia is unsettled as yet. The few studies so far published have used these diets for weight reduction in overweight children, and the lipid profile was evaluated only as a secondary endpoint. The trials of Sondike et al (RCT) and Dunlap & Bailes (pilot) demonstrated a significant decrease in LDL-C only in the low fat, high carbohydrate diet groups (69, 70). Other studies of low carbohydrate diets in overweight youths reported a significant decrease in TC, LDL-C and triglyceride levels, although not distinct from those of the low fat diet (71, 72).

Few studies have evaluated the benefits of dietary interventions in childhood on the prevalence of MetS or individual risk factors in children. The effect of dietary modification on insulin sensitivity has however been evaluated in both the DISC and STRIP studies. Starting low saturated fat diets in infancy (STRIP) improved insulin sensitivity in healthy children at 9 years of age. At 15 and 20 years HOMA-IR was lower (7.5% on average) in the intervention group than in the control group ($p = 0.0051$) (73). A follow-up study conducted in 2006–2008, 9 years after termination of the Dietary Intervention Study in Children (DISC) reported similar prevalences of MetS between control and treatment groups (60). However, after adjustment for non-dietary variables, mean systolic BP in the intervention and control group participants were 107.7 and 110.0 mm Hg, respectively ($p = 0.03$), whereas mean fasting plasma glucose levels were 87.0 and 89.1 mg/dl (4.8 and 4.9 mmol/L), respectively ($p = 0.01$). Intervention group participants also had lower concentrations of large very-low-density lipoprotein particles, a marker of hepatic insulin resistance, compared with control group participants. The conclusion emerging from this study is that consumption of a diet lower in fat and higher in fibre during childhood and adolescence may benefit glycaemic control and blood pressure in the long term.

3.3 Nutritional Intervention at the Population Level and in Those at High Risk

Cholesterol-lowering therapy in children with hypercholesterolaemia, including FH, starts with dietary intervention and life-style modification. The Scientific Statement from AHA for the treatment of high risk lipid abnormalities in children and adolescents advocates the use of dietary treatment also as adjuvant to pharmacological treatment (23). Existing paediatric guidelines are based on a consensus report originally published in 1992 by the NCEP Expert Panel on Blood Cholesterol Levels in Children and Adolescents (24). The NCEP has recommended a two level nutritional approach, which has been adopted, with some differences, by both AAP and AHA: a *population-based approach* aimed at shifting the population distribution of cholesterol levels and an *individualized approach* for high risk groups who needed further monitoring and management (26) (**Table 10**).

Table 10
NCEP recommended nutritional approach, *population-based* and *individualized* approach

Diet component	Population-based approach	Individualized approach
Total fat	Less than 30% of total calories	Less than 30% of total calories
Saturated fats	Less than 10% of total calories	Less than 7 % of total calories
Mono unsaturated fats	10-15% of total calories	10-15% of total calories
Polyunsaturated fats	Up to 10% of total calories	Up to 10% of total calories
Carbohydrates	50-60% of total calories	50-60% of total calories
Protein	10-20% of total calories	10-20% of total calories
Cholesterol	300 mg per day or 100 mg/1000 kcal	200 mg per day or 75 mg/1000 kcal
Total calories	Maintain proper growth and development	Maintain proper growth and development

The cornerstone recommendation of the *population-based approach* is that all healthy children >2 years of age adopt a fat- and cholesterol-restricted diet according to the last year's Dietary Guidelines for Americans (74). The AAP guidelines place an emphasis on improving the quality of dietary fat rather than reducing total fat consumption and advocate lowering the recommended age for dietary initiation of a low-fat diet in high-risk groups (48-50). Although fat-restricted diets are generally not recommended for children under 2 years of age, the AAP guidelines suggest considering the use of low-fat dairy products for high risk children aged 1 year and older with a BMI \geq 85th percentile or a family history of obesity, dyslipidaemia, or CVD. Evidence from the ongoing STRIP study shows that the growth and neurological development of children aged 7 months and upwards who were maintained on a low fat diet was comparable to controls. Consumption of a wide variety of foods was recommended to achieve nutrient needs and with a goal to achieve an average daily intake of <10% of total calories from saturated fat with <30% from total fat and intake of <300 mg/d dietary cholesterol (former Step 1 diet) (75). The general dietary recommendations of the AHA for those aged 2 years and older stress a diet that primarily relies on fruits and vegetables, whole grains, low-fat and non-fat dairy products, beans, fish, and lean meat. These general recommendations echo other recent public health dietary guidelines in emphasizing low intakes of saturated and *trans* fatty acids, cholesterol, added sugar and salt, energy intake

and physical activity appropriate for the maintenance of a normal weight for height, and adequate intake of micronutrients. The 2010 and 2015-2020 *Dietary Guidelines for Americans* (for those 2 years of age and older) provide important supporting reference information with regard to overall diet composition, appropriate caloric intakes at different ages, macronutrients, micronutrients, portion size and food choices (74).

3.4 Effect of a Low Fat Diet in Childhood on Future CVD in Adulthood

The evidence that a low saturated fat, low cholesterol diet in childhood will prevent CVD in adulthood can only be inferred from epidemiological studies, where children from countries with a lower prevalence of CVD had lower TC levels than those children from countries with higher CVD and TC levels (76).

Children with heterozygous FH have been shown to have abnormalities on non-invasive vascular assessments, including greater carotid intima medial thickness and abnormal arterial endothelial function (77). These have been used as surrogate markers for atherosclerosis, and lipid-lowering interventions, including low fat, low cholesterol diets have been shown to improve these abnormalities. Evaluation of flow-mediated dilatation at 11 years in children participating in the STRIP study, where a low saturated fat diet was introduced in infancy and maintained during the first decade of life, was associated with enhanced endothelial function in boys, but not in girls, effects mediated in part by the diet-induced reduction in TC (78). In addition, in the same Finnish study, the children showed improved insulin sensitivity at 9 years, and being overweight was less prevalent in the intervention group (10%), than in the controls (19%).

Data on cardiovascular health metrics (smoking, BMI, physical activity, diet, TC, BP, plasma glucose) of participants in the STRIP study has been reported recently (79). At 15, 17 and 19 years, adolescents in the control group had lower ideal cardiovascular health (≤ 3 metrics) when compared with the adolescents from the intervention group (risk ratio=1.35; 95% confidence interval=1.04–1.77). The number of ideal cardiovascular health metrics was inversely associated with aortic IMT ($p<0.0001$) and directly associated with elasticity ($p=0.045$). This study provides novel data that cardiovascular health, according to the AHA definition, can be promoted in adolescents and is associated with surrogate markers of atherosclerosis—aortic IMT and elasticity.

3.5 Nutritional Supplements

There has been a great deal of interest in dietary supplements and complementary medicines, although few have been subjected to rigorous clinical evaluation. Obviously, complementary medicines and dietary supplements and modifications should be supported by rigorous clinical trial evidence before being adopted as acceptable therapies for the management of hyperlipidaemia in children. **Table 11** presents a summary of studies on several nutritional supplements.

Table 11
Summary of studies on several nutritional supplements for paediatric hyperlipidaemia

Study	Intervention	Results
Williams CL (80) <i>J Am Coll Nutr</i> 1999;18:572	Plant stanols 3g/day, 13 weeks Cross-sectional 19 children, 2-5 years old	TC decrease of 19.9 mg/dL ($p < .01$) LDL-C decrease of 14.6 mg/dL ($p < .05$) No change in HDL-C, TG
Tammi A (81) <i>Acta Paediatr</i> 2002; 91: 1155	Plant stanols 1.5g/day DBPC, crossover 81 children	Boys: TC decreased by 6% ($p < 0.01$) LDL-C decreased by 9% ($p < 0.01$) Girls: TC decreased by 4% ($p < 0.05$) LDL-C decreased by 6% ($p < 0.05$)
Engler MM (82) <i>Am J Cardiol</i> 2005;95:869	1.2 g/d DHA, 6 weeks 20 children, 9-19 years	No changes in TC, LDL, HDL, and TG
Engler MM (83) <i>Int J Clin Pharmacol Ther</i> 2004;42:672-9	1.2 g/d DHA, 6 weeks 20 children, 9-19 years	Improved FMD ($p < 0.001$) Increase of TC, HDL-C
McCrindle BW (84) <i>Arch Pediatr Adolesc Med.</i> 1998;152:1089	Garlic extract, 6 weeks 30 children, 8-18 years	No changes in TC, LDL, HDL, and TG
Weghuber D (85) <i>Br J Nutr.</i> 2008 ;99:281	Soy protein 0.25-0.5 g/kg, 3 months 23 children, 4-18 years	Significant decrease vs baseline TC by 7.7% ($p < .002$) LDL-C by 6.4% ($p < .0003$) No change in HDL-C, TG
Wong H (86) <i>JAAMA</i> 2013;167:708 <i>Pediatr</i>	Flaxseed 30-g/d, 4-week PCRB study 32 children	HDL-C reduction by 15% TG increase by 26% No change in TC, LDL-C
Garaiova I (87) <i>Nutrition Journal</i> 2013, 12:7	Plant sterols esters (1.3g), Fish oil (EPA+DHA 1000 mg) Vitamins B12,B6, folic, coenzymeQ10 25 children, 16 weeks	Reduction of TC, LDL-C, VLDL-C ($p < 0.05$) TG decreased by 16.7% (NS) No changes in CRP, HDL-C, ApoA1
Guardamagna O (88) <i>Nutrition</i> 2013;29:1060	Glucomannan 500mg/d, 8 weeks 36 children, 6-15 years DBPC cross over	Girls: TC reduced by 6.1% ($p < 0.011$) LDL-C reduced by -9% ($p < 0.015$) No change in boys
Davidson MH (89) <i>Am J Clin Nutr</i> 1996;93:96-102	Psyllium-enriched cereal 6 weeks 25 children, 6-18 years DB cross over	TC reduced by 12.1 mg/dL (7%)($p = 0.03$) LDL-C reduced by 10.9mg/dL ($p = 0.01$) No change in boys

Stanols. Partial substitution of dietary fat consumption with margarines high in plant stanol esters can reduce LDL-C by an additional 10-15% when included in a low-fat diet. The proposed mechanism of action of plant stanols and sterols is in lowering the absorption of dietary cholesterol. Plant stanols and sterols may be added to a number of food products,

including spreads and margarine, orange juice, yogurt drinks, cereal bars, and dietary supplements. A clinical trial of plant stanol ester margarine in 81 children showed that LDL-C levels were lowered by a mean of 7.5%, with good tolerance (81). The most important safety concern with these products is that they may also result in decreased absorption of fat-soluble vitamins and beta-carotene. Formal recommendation of their use for children awaits clinical trial data.

Soy protein. The source of dietary protein has been shown to have a significant influence on the concentrations of plasma cholesterol and lipoproteins, with soy protein having a hypocholesterolaemic effect when compared with casein (85). In studies on hypercholesterolaemic adults, substitution of mixed animal proteins with soy-protein induced moderate to marked plasma cholesterol decreases. Small studies of dietary alterations in hyperlipidaemic children have shown that substitution with soy-based protein may increase HDL-C and lower VLDL levels and triglyceride and may lower LDL-C levels. At the present time, however, adjunct dietary intervention with soy protein is not advocated for patients with dyslipidaemia.

Omega-3 fatty acids. Diet supplementation with ω -3 fatty acids has been advocated, but is not supported by randomized controlled clinical trials. Compared with placebo, supplementation of a low-fat diet with omega-3 fatty acid, docosahexaenoic acid 1.2 g/day, did not lower LDL-C, but changed the distribution between LDL subclasses with shifts toward less dense LDL particles, 91% increase in the largest LDL and a 48% decrease in the smallest LDL subclass as compared to placebo (82,83).

Dietary fibre. Increased intake of soluble fibre is recommended as an adjunct to the reduced intakes of saturated fatty acids and cholesterol. Water-soluble fibres, such as psyllium, can provide an additional 5% to 10% lowering effect on LDL-C. The proposed mechanism of action of fibre is thought to be by binding to bile acid cholesterol, and its removal from the enterohepatic circulation. Studies reporting the effect of water-soluble supplemental fibres such as psyllium have divergent conclusions. Some have shown a reduction in LDL-C concentration by approximately 5-10%. Davidson and colleagues performed a crossover clinical trial in 26 hyperlipidaemic children, and showed a 7% reduction in LDL-C with the psyllium-enriched compared to the control group (89). In contrast, Dennison and colleagues did not show any benefit on lipid levels in a similar crossover clinical trial in 20 hyperlipidaemic children supplemented with psyllium-enriched cereal (64).

Garlic. Garlic extract preparations have been marketed for the treatment of hyperlipidaemia, although evidence of a beneficial effect on the lipid profile has not been noted in independent clinical trials. A placebo-controlled, double-blind clinical trial conducted in 30 children with familial hyperlipidaemia using a commercially available garlic extract, showed no clinically important effect on the lipid profile or any other cardiovascular risk factor (84).

3.6 Safety of Dietary Therapy in Infants, Children and Adolescents

Data from the ongoing Special Turku Risk Intervention Program (STRIP) conducted in infants as young as 7 months of age, and from the DISC study conducted in children aged 8 to 10

years throughout adolescence, have demonstrated that these dietary recommendations are safe and do not interfere with normal growth, development, and sexual maturation (90,91). Failure to thrive, however, has been demonstrated in children under 2 years of age who eat fat-restricted, low energy diets. Thus, implementation of these diets should be very carefully supervised in children in this age group. In addition, in some studies, there were lower intakes of calcium, zinc, vitamin E, and phosphorus on low-fat diets (92, 93).

Therefore, although normal growth could be achieved and maintained on low-fat diets, attention needs to be paid to ensure adequate intake of these key nutritional elements. Medical and nutritional support is necessary to reinforce good dietary behaviour and to ensure nutritional adequacy.

Lastly, people with hypercholesterolaemia may be susceptible to potentially detrimental psychological and nutritional consequences of their dietary treatment. However, so far, few studies have assessed the quality of life of children with dyslipidaemia on dietary intervention (94, 95).

3.7 Nutritional Assessment and Counselling

Dietary intervention should be preceded by a detailed nutritional assessment including anthropometry and review of the current eating patterns. In general, dietary recommendations should be consistent with good nutrition, aimed at a balanced energy intake to ensure optimal growth and development while preventing obesity. Close guidance and follow up by a qualified dietician should assist the child and family alike. As children begin to consume fewer calories from fat, the missing calories should be replaced by eating more grain products, fruits, vegetables, calcium-rich foods (low-fat milk products), or protein-rich foods (lean meat, poultry, fish). No single food item provides all essential nutrients, thus, choosing a wide variety of food from all the food groups will ensure an adequate diet.

The home environment aids children and adolescents make the right nutritional choices and maintain a healthful diet. Parents should be encouraged to act as a role model for their children and all family members should consume a healthy diet. Dieticians should guide children and their families in making healthy choices at school, and in fast-food restaurants. Care should be taken as some parents and their children may implement an extremely low-fat diet, leading to nutritional insufficiency and subsequent growth failure (93, 94).

3.8 Follow up

The reduction in fat intake, if done without professional monitoring and counselling, could potentially lead to a deficiency of essential fatty acids and fat soluble vitamins and a reduction in the overall energy content of the diet, which has implications for satiety and growth in children who have relatively high energy requirements. An increase in the carbohydrate content of the diet may lead to raised blood levels of triglyceride. Children and adolescents placed on a low-fat diet should have height and weight assessments every 6 months to ensure that linear growth is not compromised. To date, the exact percentage of dietary intake from fat that supports normal growth and development while maximally reducing atherosclerosis risk needs clarification, especially when the effect of carbohydrate intake in children is ill defined.

Dietary Management of Hypertriglyceridaemia

Elevated TG levels are very responsive to weight loss, diet composition, and exercise. Most importantly, in overweight and obese children and adolescents with elevated TG levels, even small amounts of weight loss are associated with significant decreases in TG levels and increases in HDL-C levels (96).

In adults with hypertriglyceridaemia, a low-carbohydrate, high-fat diet (40% carbohydrate, 39% total fat, 8% saturated fat, 15% monounsaturated fat) significantly decreased TG by a mean of 63%, with associated mean increases in LDL-C of 22% and HDL-C of 8% (97).

In children, a 12-month follow-up study of 21-month old children with elevated TG levels treated with a carbohydrate-restricted diet showed a decrease in sugar and carbohydrate intakes associated with a decrease in TG from a mean of 274.1 ± 13.1 mg/dL before treatment to 88.8 ± 13.3 mg/dL after 12 months (98).

The analysis of adolescents from NHANES, reported a significant inverse association between the overall diet quality score and the prevalence of the metabolic syndrome components. There was also a trend toward a lower prevalence of these components, including elevated TG in adolescents with high activity levels, although this was not significant. The concept of glycaemic load has also been evaluated in the setting of obesity and dyslipidaemia in adolescents and adults. The glycaemic index is a measure of the blood glucose response to a 50 g portion of a selected carbohydrate; the glycaemic load is the mathematical product of the glycaemic index and the carbohydrate amount (99). In adolescents and young adults, there is evidence that low glycaemic-load diets are at least as effective as low-fat diets in achieving weight loss, with decreased TG and increased HDL in subjects on the low glycaemic-load diet (100).

In children with severe hypertriglyceridaemia for whom diet and exercise interventions are insufficient, there are nutraceutical and medication options that can be considered (**Fig. 5**).

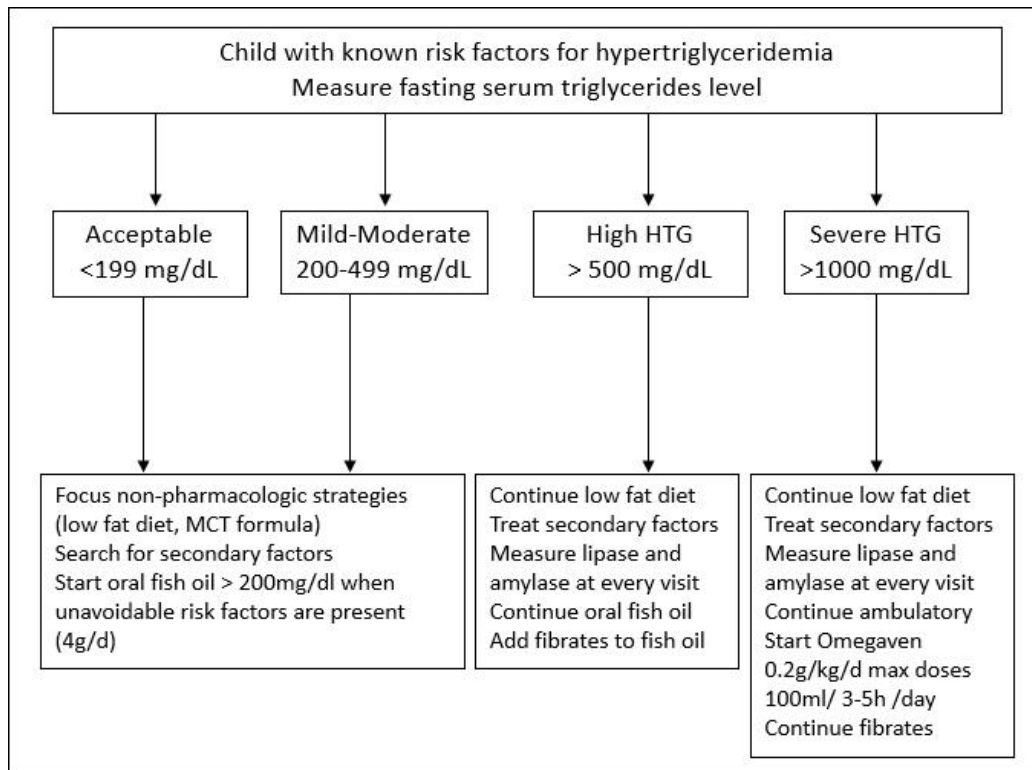


Fig. 5. Algorithm for the management of a child with HTG

A recent systematic review demonstrated that omega-3 fish oil capsules are both safe and effective in adults, reducing TG by 30–45 percent, with significant associated increases in HDL-C (101). In adults, fibrates have been used to lower TG levels, and a small series in children demonstrated effective reductions in TG levels and an associated increase in HDL-C levels. Finally, niacin has been used extensively in adults, but there is limited experience in children, with a single series demonstrating a high rate of side effects. The use of either fibrates or niacin in youths should be undertaken only with the assistance of a lipid specialist. For children, the efficacy and safety of omega-3 fish oil was investigated in a double-blind randomized trial of fish oil, 4g/day for 8 weeks, in 42 children with hypertriglyceridaemia. Fish oil treatment decreased TG levels but not significantly compared to placebo (102). Another trial in 25 children with HTG reported a similar decrease in TG levels in the treatment group compared to placebo group (103).

Children with sustained TG levels ≥ 500 mg/dL present a rare and serious clinical problem that is usually associated with an underlying genetic defect (LPL deficiency, HL deficiency, or apoC-II deficiency). They are at high risk for pancreatitis beginning in infancy. These children require a very low-fat diet (<10 percent fat) undertaken with a nutritionist's assistance to ensure adequate calories and intake of essential fatty acids. Medium-chain TG, which are absorbed directly into the portal system and do not require chylomicrons for transport to the liver, can have a significant lowering effect on TG levels, especially in those with defective or deficient LPL. Patients with either LPL or apoC-II deficiency do not respond to lipid-altering medications, but patients with HL deficiency will respond to fibrates, niacin, or statins.

The Cardiovascular Health Integrated Lifestyle Diet (CHILD) was developed to assist in management of these patients (**Table 12**). CHILD 1 is the first stage in dietary change for children with identified dyslipidaemia, overweight and obesity, risk factor clustering, and high-risk medical conditions who may ultimately require more intensive dietary change. CHILD 1 is also the recommended diet for children with a positive family history of early CV disease, dyslipidaemia, obesity, primary hypertension, diabetes, or children exposed to smoking in the home. CHILD 2-LDL and CHILD 2-TG are dietary interventions recommended in children with hypercholesterolaemia or hypertriglyceridaemia and elevated serum LDL-C and TG respectively after 6 months of CHILD 1 implementation and as an adjuvant to pharmacological treatment. Any dietary modification must provide all the nutrients needed for optimal growth and development.

Table 12
Cardiovascular Health Integrated Lifestyle Diet – CHILD (28)

CHILD 1	CHILD 2 –LDL 2-21 years	CHILD 2-TG 2-21 years
10–30% calories from protein	10–30% calories from protein	10–30% calories from protein
45–65% calories from CHO	45–65% calories from CHO	45–65% calories from CHO
Total fat 30% of kcal/EER Transition to reduced-fat milk (2% to fat-free) – after 12 months Saturated fat 8–10% of kcal/EER Avoid trans fat as much as possible Monounsaturated and polyunsaturated fat up to 20% kcal/EER Cholesterol < 300 mg/d	25-30% of calories from fat, ≤ 7% from saturated fat, ~10% from monounsaturated fat; < 200 mg/d of cholesterol; Avoid trans fat as much as possible.	25-30% of calories from fat, ≤ 7% from saturated fat, ~10% from monounsaturated fat; < 200 mg/d of cholesterol; Avoid trans fat as much as possible
Limit/avoid sugar-sweetened beverage intake Encourage water	Limit/avoid sugar-sweetened beverage intake Encourage water	Decrease sugar intake: Replace simple with complex CHO No sugar-sweetened beverages
Limit 100% fruit juice to less than 4 oz/d (100ml).	Limit 100% fruit juice to less than 4 oz/d (100ml).	Limit 100% fruit juice to less than 4 oz/d (100ml).
Limit sodium intake	Limit sodium intake	Limit sodium intake
Consider DASH-type diet*	Consider DASH-type diet*	Consider DASH-type diet*
Encourage dietary fibre from foods: Age plus 5 g/d.	Encourage dietary fibre from foods: Age plus 5 g/d.	Encourage dietary fibre from foods: Age plus 5 g/d.

Teach portions based on EER for age/gender/activity	Teach portions based on EER for age/gender/activity	Teach portions based on EER for age/gender/activity
	Plant sterol esters and/or plant stanol esters up to 2 g/d	Increase dietary fish to increase omega-3 fatty acids
	Refer to a registered dietitian for family medical nutrition therapy	Refer to a registered dietitian for family medical nutrition therapy
	As in all children, 1 hour/day (h/d) of moderate-to-vigorous physical activity and < 2 h/d of sedentary screen time are recommended.	As in all children, 1 hour/day (h/d) of moderate-to-vigorous physical activity and < 2 h/d of sedentary screen time are recommended

*Dietary Approaches to Stop Hypertension (DASH). The DASH diet focuses on increased fruits and vegetables, low-fat dairy products, and whole grain foods and meets all nutrient and energy requirements for children in this age range. Dietary sodium intake should also be limited.

4. Summary of Recommendations for Screening and Treatment of Dyslipidaemia in Children and Adolescents

- All healthy children >2 years of age should adopt a fat- and cholesterol-restricted diet according to the Dietary Guidelines for Americans;
- Selective or universal screening are still a matter of debate and national paediatric associations' recommendations should be followed ;
- The recommended ages for universal screening are 9-11 years and 17-21 years and non-fasting blood samples are recommended;
- For selective screening: fasting serum lipid profiles should be performed in a selected group of children older than 2 years, preferably before 10 years and including: 1) children with a family history of dyslipidaemia or premature CAD, 2) children with disorders associated with secondary dyslipidaemia and 3) children affected by risk factors, eg overweight, hypertension, diabetes mellitus;
- For children whose LDL-C level remains >3.35 mmol/L (>130 mg/dL) while compliant with the fat- and cholesterol-restricted diet, a more restrictive diet should be implemented. This diet further limits saturated fat intake to <7% of total caloric intake and cholesterol intake to <200 mg/d;
- Close guidance and follow up by a qualified dietician should be in place to assist the child and family constantly;
- LDL-C lowering drug therapy is recommended only in those children >8-10 years of age, who after an adequate 6- to 12-month trial of diet therapy still have extremely high LDL-C levels (**Fig. 3, 4**).

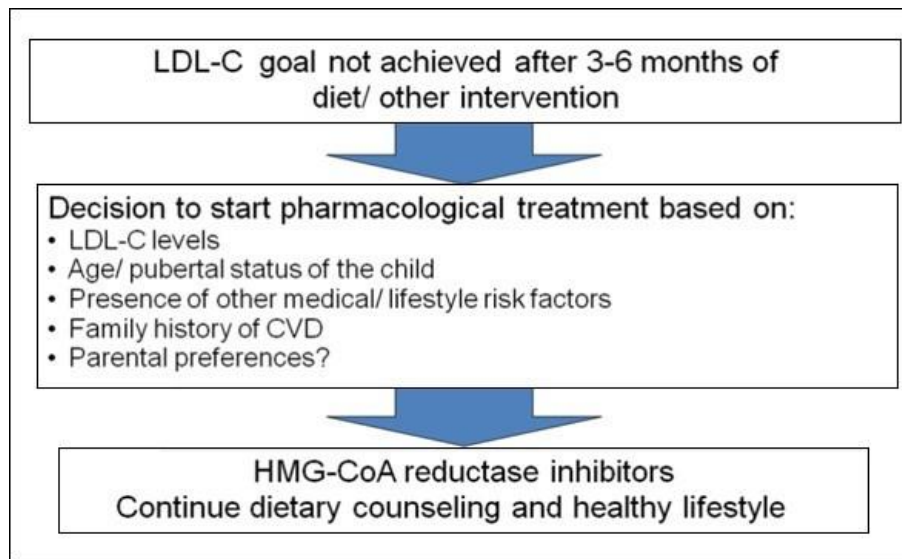


Fig. 3 Algorithm for investigation, treatment and follow up (2)

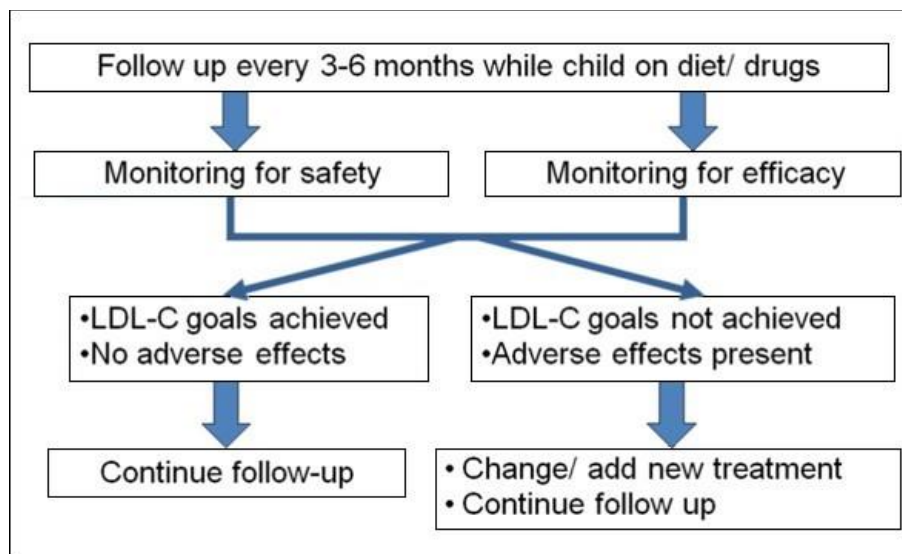


Fig. 4 Algorithm for investigation, treatment and follow up (3)

5. Dietary and Lifestyle Interventions, Summary of AHA and AAP Recommendations

- Adequate nutrition should be achieved by eating a wide variety of foods;
- Total energy intake, should be sufficient to support normal growth and development and maintain/achieve appropriate body weight;
- No decrease in total protein is recommended;
- Total fat should provide no more than 30% but no less than 25% of total calories;
- In children aged 12 months to 2 years who are overweight, obese, or have a family history of obesity, dyslipidaemia, or cardiovascular disease, the use of reduced fat milk/ dairy products deserve careful consideration;

- Saturated fat should provide less than 10% of total calories for all children and less than 7% for children in high-risk groups;
- Eliminate *trans*-fats and replace them with polyunsaturated fats, and include fish, especially oily fish (at least twice a week);
- Children should consume no more than 100mg/1000 calories of cholesterol per day and less than 75 mg/1000 calories cholesterol per day if they belong to the high risk group;
- Children should consume at least 5 daily servings of vegetables or fruits together with whole grain bread/cereals; simple sugars should be replaced with complex carbohydrates
- All children should eat adequate amounts of dietary fibre (age+5 g/ day) up to 20 grams
- Reduce salt intake, including salt from processed food;
- The diet should be implemented under the counselling and monitoring of a nutritionist (physician or a dietician);
- Physical activity (time spent in active play) should be at least 1 hour/ day, whereas screen time (television, computer or video game) should not exceed 2 hours/day.

Conclusions

The progression of atherosclerosis from childhood fatty streaks to clinically significant fibrous plaques during young adulthood was established in the 1980s by the publication of post mortem studies from the Bogalusa Heart Study and the PDAY study. These studies have shown that atherogenesis early in life is associated with the traditional risk factors for CAD and that these risk factors tend to track into adulthood. Since many lifestyle changes are difficult to achieve in adulthood and even harder to maintain over the long term, it seems reasonable to attempt to alter these risk factors early in life.

While lifestyle modification is the mainstay of treatment, sometimes it is not sufficient to achieve the desired cholesterol levels, and drug therapy may be warranted. Nevertheless, with the increasing use of drugs in the treatment of children with hypercholesterolaemia, it must be emphasized that dietary and drug treatments are synergistic, and that dietary and life-style modifications must not be abandoned after the initiation of drug therapy.

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